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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/717,321	11/20/2000	Bonnie Gould Rothberg	15966-601 (Cura 101)	1397

30623 7590 12/31/2002

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
LOEB, BRONWEN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/717,321	Applicant(s) ROTHBERG ET AL.	
	Examiner Bronwen M. Loeb	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-51 and 54-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-51 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3&8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is in response to the communication filed 16 October 2002 in which claims 48 and 54-56 were amended and claims 1-47, 52 and 53 were cancelled.

It is noted that the substitute specification filed 25 April 2002 was entered upon receipt of the marked up version of it, filed 27 June 2002.

Claims 48-51 and 54-56 are pending.

Election/Restrictions

1. Applicant's election without traverse of Group IXX, claims 48-51 and 54-56 as read on RISKMARKER 1, in Paper No. 18 is acknowledged.

Claim Objections

2. Claim 48 is objected to because of the following informalities: Claim 48 recites "a RISKMARKER 1 nucleic acid and their complements" which is improper grammer; "their complements" should be amended to recite "its complement". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 51 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claim is very broad. Claim 51 encompasses any pharmaceutical composition comprising a RISKMARKER 1 nucleic acid.

The nature of the invention is a pharmaceutical composition comprising a nucleic acid sequence in rat liver which is differentially expressed in response to various NSAIDs and whose expression may be used to predict the liver toxicity of new NSAIDs. A pharmaceutical composition implies that the composition is used for therapeutic effect; delivery of a nucleic acid in vivo or ex vivo for therapeutic purpose constitutes gene therapy. Thus, the claimed composition represents a medicament for gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature

(1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al , p. 33, col. 1, 1st paragraph.

The relative skill of those in the art of DNA technology is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2): 1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for a gene therapy pharmaceutical composition. The specification does not disclose the biological function of RISKMARKER 1, but rather, merely notes some homology to the 3' UTR of human rac1. There is no evidence that RISKMARKER 1 is the 3'UTR of a rat homolog of rac1. While its utility in predicting hepatotoxicity of NSAIDs is evident, there is no evidence that RISKMARKER 1 or its complement could provide any therapeutic effect in any disease. Furthermore, if indeed RISKMARKER 1 is part of the 3' untranslated regulatory region of gene, it is unclear how a nucleic acid encoding only this part of the gene could be used in any therapeutic manner. Furthermore, the specification discloses no specific diseases for which the claimed medicament can be used. There is no direction provided as to how to overcome the obstacle to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression.

There are no working examples disclosed.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine what the biological function any polypeptide encoded by a RISKMARKER 1 nucleic acid, then determine what condition might be treated by a RISKMARKER 1 nucleic acid, what effect exogenous transgene expression of a RISKMARKER 1 nucleic acid would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver

the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make and/or use the claimed pharmaceutical composition.

5. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 48-51 and 54-56 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 is vague and indefinite in reciting "RISKMARKER 1 nucleic acid". This phrase is not a term of art nor is it clearly defined by the specification. Does it consist of SEQ ID Nos. 1, 2, 15 and 17 as is possibly taught in the specification on pp. 7-9?

Claim 54 is vague and indefinite because it recites the intended use of the kit but it does not actually recite any components of the kit.

Claim 55 is vague and indefinite because it recites the intended use of an array but it does not actually recite any components of the array.

Claims 54-56 are vague and indefinite in reciting "nucleic acid sequences selected from the group consisting of RISKMARKER 1" because it is unclear what nucleic acid sequences are in the group "RISKMARKER 1" (see also claim 48 rejection above).

Conclusion

Claims 48-51 and 54-56 are rejected. Claims 48-51 and 54-56 are free of the prior art as there is no prior art which teaches or suggests a RISKMARKER 1 nucleic acid, which has been interpreted by the Examiner to included SEQ ID NOs. 1, 2, 15 and 17. The closest prior art is accession no. BF420446, Bonaldo et al (Genome Research (1996) 6:791-806; cited in IDS Paper #8); nucleotides 66-187 of BF420446 is 100% identical to nucleotides 1-122 of SEQ ID NO. 1 (which is 123 nucleotides in length), as a sequence in a rat cDNA library. It is noted the nucleotides 1-122 of SEQ ID NO. 1 has been identified as a subset of a number of rat sequences such as AI598992 and AI412434, none of which has a C at position 123.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 11:00 AM to 7:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Customer service for Tech Center 1600 may be reached at (703) 308-0196.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

December 30, 2002

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600